History and Efficacy of Propoxyphene Products

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Overview of Presentation

- Regulatory history of propoxyphene (PPX) products
- Efficacy of PPX products
  - Original NDA submissions in 1971
  - Literature reports

Regulatory History: 1957

The first propoxyphene products were approved based on safety only under the 1938 Food Drug & Cosmetic Act (FD&C Act)

- **Darvon (propoxyphene HCl 32 mg and 65 mg)**
- **Darvon-Compound (aspirin, caffeine combination), discontinued in US**

Regulatory History: 1962

Kefauver-Harris Drug Amendments to the 1938 FD&C Act required:

- **Evidence of safety and efficacy to approve a new drug**
- **A retrospective efficacy assessment for drugs approved prior to 1962**
  - FDA established the Drug Efficacy Study Implementation (DESI) program.
  - National Academy of Science-National Research Council (NAS-NRC) assessed the efficacy of all pre-1962 drugs
- **Propoxyphene products underwent the DESI process in the 1960's**

Regulatory History: 1969

DESI notice published (amended in 1972) in *Federal Register* (FR): Darvon and its aspirin combination products were *"effective for mild to moderate pain"*

- **The conclusion was primarily based on the recommendations of the NAS efficacy report.**
- **The NAS efficacy report relied upon two review articles published in the mid-1960s (Beaver 1966 and Lasagna 1964).**

The FR publication (DESI conclusion), the NAS Efficacy Report and the published review articles are in Attachment-1 of Backgrounder-4

Regulatory History: 1971

- Propoxyphene napsylate 100 mg was approved, trade-named “Darvon-N”
- Is molar equivalent to propoxyphene HCl 65 mg
- Was bioequivalent to propoxyphene HCl 65 mg (Darvon)

Regulatory History: 1972

- **Propoxyphene/acetaminophen (PPX/APAP) combinations were approved**
  - Darvocet: Propoxyphene HCl and acetaminophen
  - Darvocet-N: Propoxyphene napsylate and acetaminophen combination
- **Efficacy trials and bioequivalence studies**
- **90% Rxs of propoxyphene are the APAP combination products in current US market**

Efficacy Data in 1971: NDAs of Darvocet and Darvocet-N

Seven single-dose efficacy trials were submitted to the Darvocet and Darvocet-N NDAs (Applicant: Eli Lilly & Company):

- **Had identical study design**
- **Conducted by 3 external investigators**
  - Lash for Studies 1, 2a & 2b
  - Bauer for Studies 3a & 3b
  - Johnson for Studies 4a & 4b

Study Design of the 7 Trials

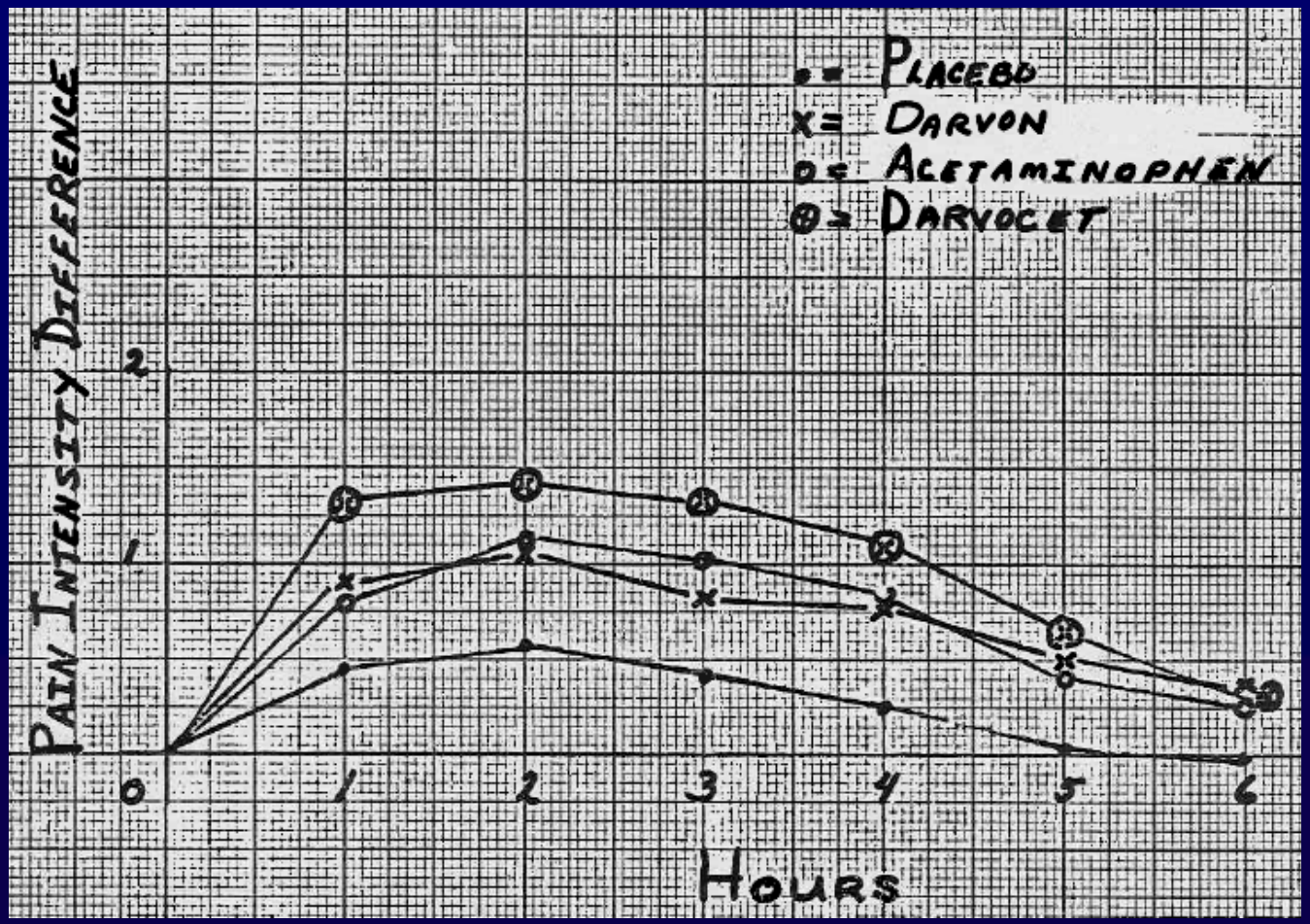
- **Randomized, double-blind, placebo-controlled, full factorial design**
- **Patients with mild to severe postpartum pain (normal delivery), n=30-48 each of 4 arms, received a single oral dose of:**
  - Propoxyphene/acetaminophen (65/650 mg)
  - Propoxyphene (65 mg)
  - Acetaminophen (650 mg)
  - Placebo
- **Efficacy was assessed hourly for 6 hours:**
  - Time-course of analgesic effects (PID, PR) over 6 hr
  - $SPID_6$ (summed pain intensity difference over 6 hrs)
  - $TOTPAR_6$ (total pain relief score over 6 hrs)

Data Presentation of the 7 Trials

- Standard deviations for the efficacy data were not provided in the original study reports.
- Detailed statistical analyses for major analgesic outcomes ($SPID_6$ or $TOTPAR_6$) were not available in the report, there were only statement by the sponsor of statistical significance.
- The only statistical details shown in the original submission are limited to the first 2-hour post dose.
- The efficacy results differed across 7 trials

Time-course of PID: Study 3a (by Bauer)

(Fig 4 in Appendix-2 of Backgrounder-4)



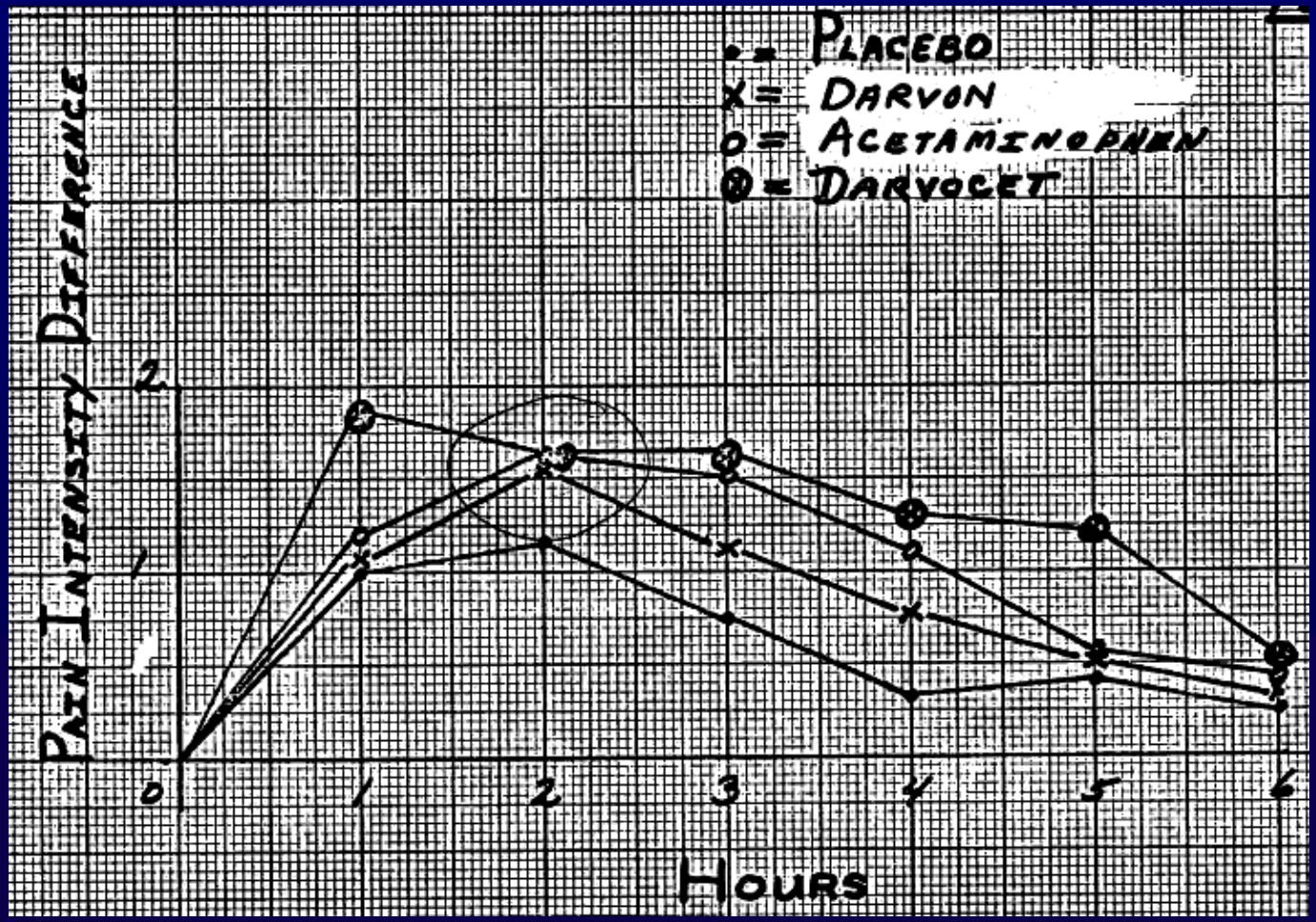
From original NDA submission of 1971

$SPID_6$ and $TOTPAR_6$ of Study 3a (by Bauer)

- PPX, APAP and the combination were statistically superior to placebo.
- PPX alone was comparable to APAP alone.
- The combination appears superior to PPX and APAP alone, but the statistical significance is unknown.

Time-course of PID: Study 3b (by Bauer)

(Fig 5 in Appendix-2 of Backgrounder-4)



From original NDA submission of 1971

$SPID_6$ and $TOTPAR_6$ of Study 3b (by Bauer)

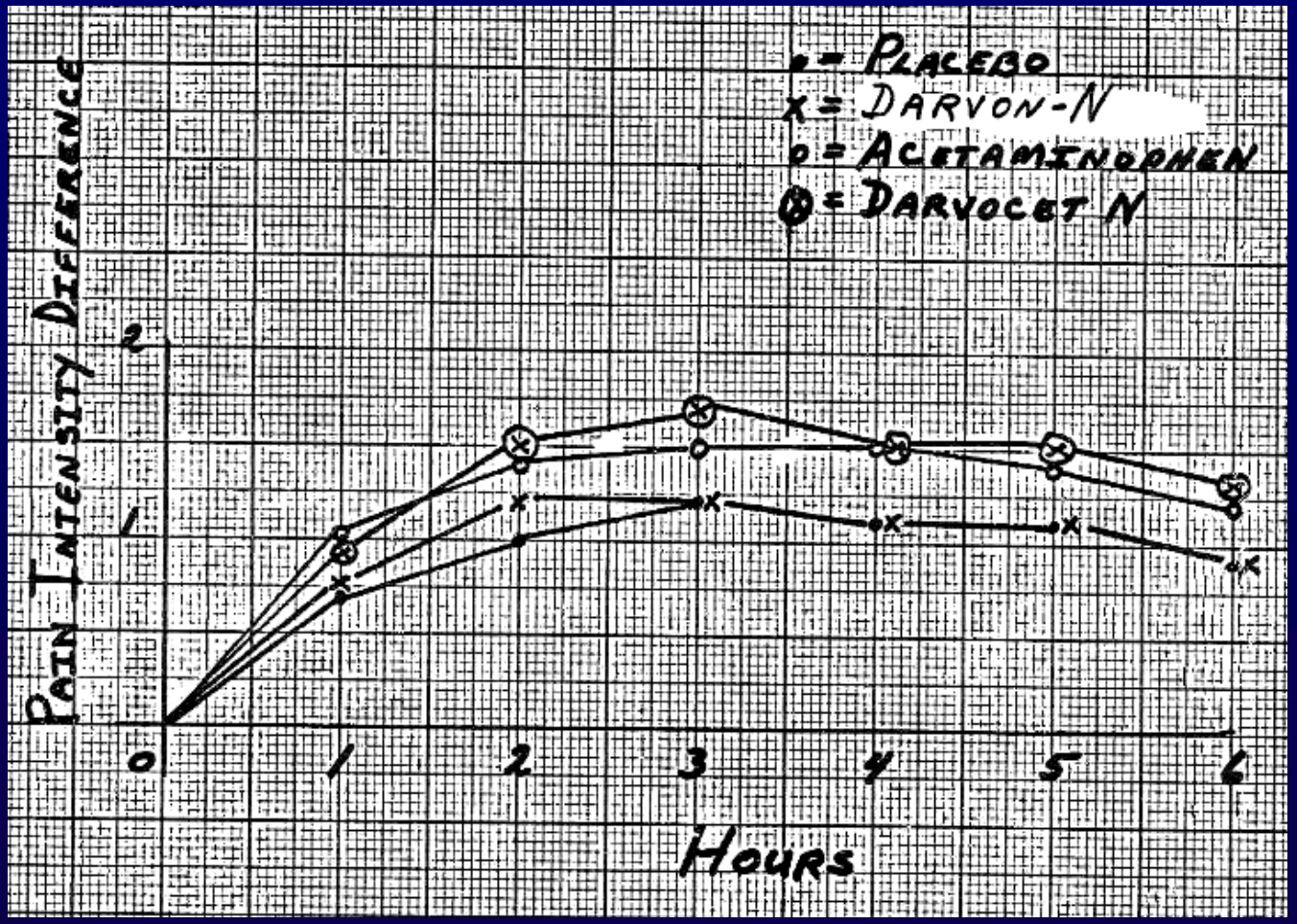
- The combination and APAP alone, but not PPX alone, were statistically superior to placebo.
- The combination was numerically superior to APAP and PPX alone.
- APAP was numerically superior to PPX.

$SPID_6$ and $TOTPAR_6$ of Studies 1, 2a, 2b, 4a and 4b

The remaining 5 trials (conducted by different investigators) had similar results:

- **PPX alone did not differ from placebo.**
- **The combination and APAP alone was statistically superior to placebo.**
- **The combination was comparable to APAP.**

Time-course of PID: Study 1 (by Lash)
(Figs 1-3 & 6-7 in Appendix-2 of Backgrounder-4)



From original NDA submission of 1971

Summary of Efficacy Trials of 1971's NDAs

- All 7 trials had the identical, single-dose, full-factorial design and were conducted using the same patient selection criteria.
- 5 of the trials showed that PPX alone had no statistically significant difference from placebo.
- APAP alone was statistically superior to placebo in all 7 trials.
- The combination was comparable to APAP alone and was statistically superior to placebo in 6 of 7 trials.

Efficacy Data in the Literature

- **Literature search: PubMed and EMBASE databases (up to Dec 2008) and citations of relevant articles**

- **Identified the most relevant publications (drugs studied, adequacy of study design and data process/report)**
  - **27 Randomized controlled trials (RCTs)**
    - **17 acute pain trials**
    - **10 chronic pain trials**
  - **10 Systematic reviews (including meta-analyses)**

  These publications are summarized in Tables 1-3 in Appendix-1 of Backgrounder-4

Published RCTs

- **Published between 1960s and 1970s**
- **The majority of the trials tested a single-dose of propoxyphene single-ingredient product in acute pain patients.**
- **There are limited literature reports of factorial design trials with the propoxyphene/APAP combination**
  - One full factorial design trial
  - A few partial factorial design trials (PPX/APAP vs. APAP alone and/or placebo)

Published Reviews

- **The reviews, including meta-analyses, all used similar published RCTs of propoxyphene products.**
- **The authors made similar conclusions:**
  - Propoxyphene, as a single-ingredient product, was a weak analgesic.
  - Propoxyphene has no or little contribution to efficacy of the APAP combination for acute pain.
  - Limited information is available to assess analgesic effects on chronic pain.
- **The conclusions were consistent with what we found from reviewing the individual trials in the literature.**

Meta-Analysis (Moore et al, 2008)

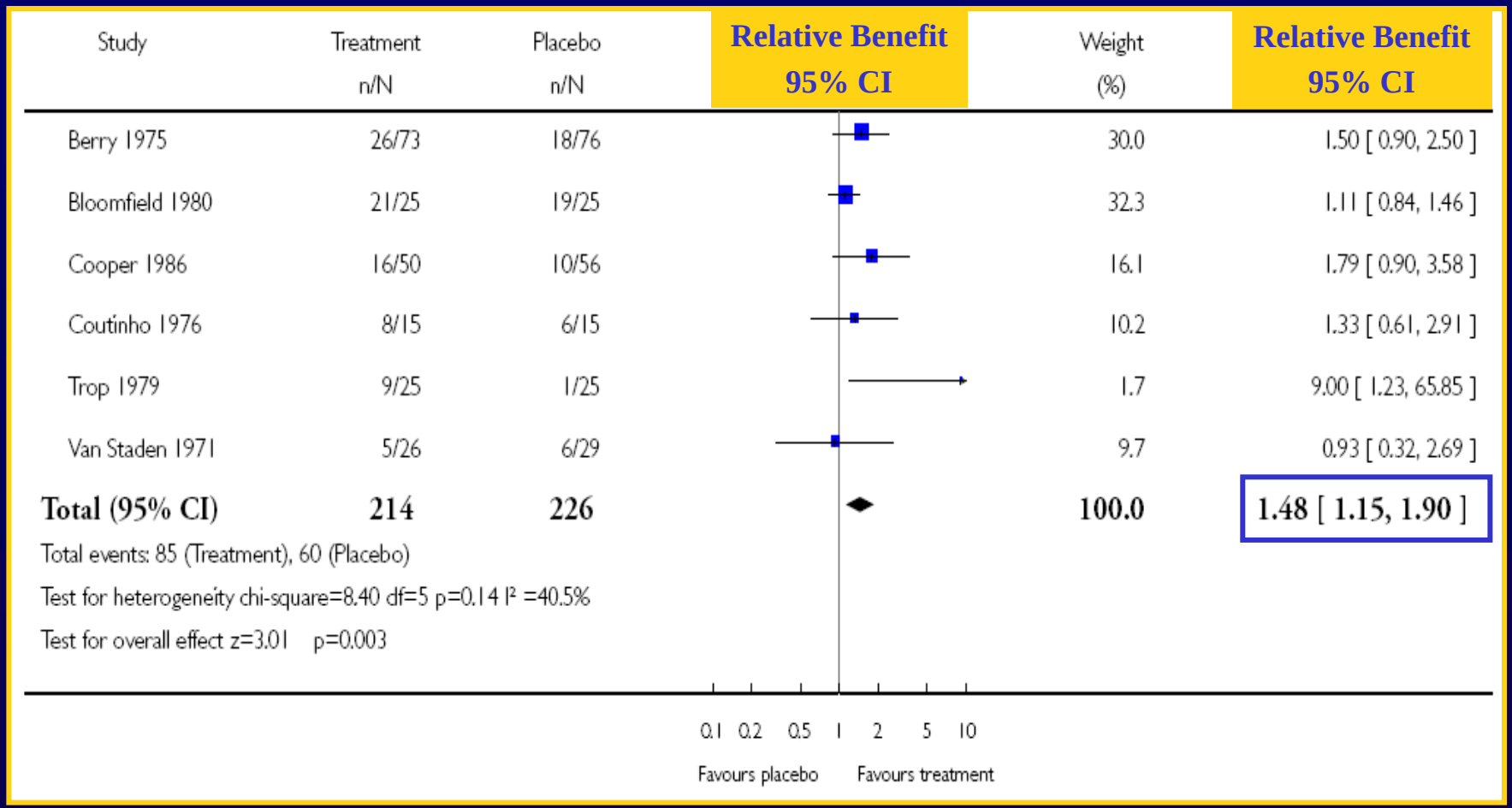
(*Cochrane Database Syst Rev*: CD001440 (3), 2008)

- **Data source:**
  - 10 published RCTs
  - 1 previous meta-analysis (8 RCTs)
- **Adult patients with post-surgical moderate-to-severe pain received a single oral dose:**
  - Propoxyphene/APAP (65/650 mg)
  - Propoxyphene (65 mg)
  - Placebo
- **Standardized PI or PR to 50% of maximum SPID or TOTPAR across trials**
- **Outcome variables:**
  - RB: Relative benefit (vs. placebo)
  - NNTB: number-needed-to-benefit
  - Re-medication within 4-8 hours

Meta-Analysis (Moore et al, 2008)

(*Cochrane Database Syst Rev*: CD001440 (3), 2008)

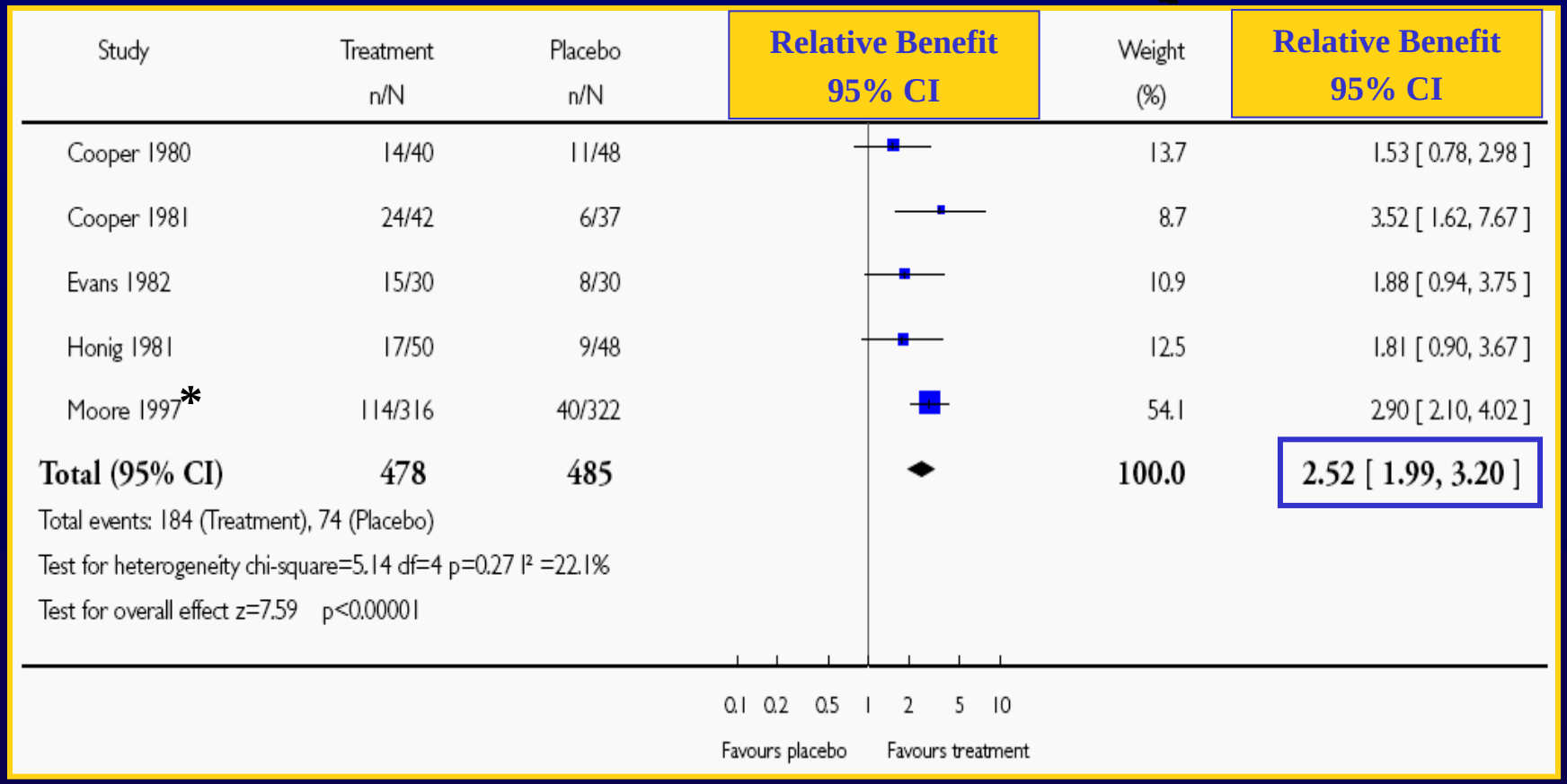
Propoxyphene *vs.* placebo



Meta-Analysis (Moore et al 2008)

(*Cochrane Database Syst Rev*: CD001440 (3), 2008)

PPX/APAP combination *vs.* placebo



*** Moore 1997**: *Pain* 69 (3): 287-94 (single patient data meta-analysis of 8 trials)

Meta-Analysis
(Po & Zhang: *BMJ* 1997)

- **Data source:**
  - 26 published RCTs
- **Adult patients with postsurgical pains received a single oral dose:**
  - PPX/APAP combination (65/650mg)
  - APAP (650 or 1000 mg)
  - Placebo
- **Outcome variables**
  - Standardized SPID
  - Response Rate Ratio (treatment vs. control)
- **Compare between the combination and APAP:**
  - Direct: head-to-head for factorial studies
  - Indirect: placebo-referenced cross studies

Meta-Analysis: Standardized SPID
(Po & Zhang: *BMJ* 1997)

- Difference in pooled SPID between the combination and APAP was not statistically significant.

- The combination and APAP were statistically superior to placebo in pooled SPID but with overlapping 95% CI, suggesting APAP was a primary contributor to the combination

Overall Summary

Based on the evidence from DESI process, original NDA submissions and our literature review, we found that:

- **Propoxyphene shows weak analgesic effects in some acute pain trials.**
- **The contribution of propoxyphene to the analgesic effects of the combination is variable across acute pain trials.**
- **With regard to chronic pain, the NDAs contain no data and there are insufficient data in the literature to assess the analgesic effects of propoxyphene products.**